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(21) International Application Number: PCT/CA93/00201 (22) International Filing Date: 19 May 1993 (19.05.93) (30) Priority data: 07/885,758 19 May 1992 (19.05.92) US 08/057,968 7 May 1993 (07.05.93) US (71) Applicant (for all designated States except US): WESTAIM TECHNOLOGIES INC. [CA/CA]; Box 1000, Fort Saskatchewan, Alberta T8L 3W4 (CA). (72) Inventors; and (75) Inventors/Applicants (for US only) : BURRELL, Robert, Edward [CA/CA]; 112 Village Downs, Sherwood Park, Alberta T8A 4L6 (CA). MORRIS, Larry, R. [CA/CA]; #807, 11007 - 83rd Avenue, Edmonton, Alberta T6G 0T9 (CA).		(74) Agent: OGILVIE AND COMPANY; #1400 Metropolitan Place, 10303 Jasper Avenue, Edmonton, Alberta T5J 3N6 (CA). (81) Designated States: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: ANTI-MICROBIAL COATING FOR MEDICAL DEVICES (57) Abstract <p>Anti-microbial coatings and method of forming same on medical devices are provided. The coatings are formed by depositing a biocompatible metal by vapour deposition techniques to produce atomic disorder in the coating such that a sustained release of metal ions sufficient to produce an anti-microbial effect is achieved. Preferred deposition conditions to achieve atomic disorder include a lower than normal substrate temperature, and one or more of a higher than normal working gas pressure and a lower than normal angle of incidence of coating flux. Anti-microbial powders formed by mechanical working to produce atomic disorder are also provided. The invention extends to other metal coatings and powders similarly formed so as to provide enhanced solubility.</p>		

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1 **"ANTI-MICROBIAL COATING FOR MEDICAL DEVICES"**

2 **FIELD OF THE INVENTION**

3 This invention relates to methods for preparing modified materials such as metal
4 coatings or powders in a form such that metal species are released on a sustainable basis at
5 an enhanced rate. In a particular aspect, the invention relates to methods of forming anti-
6 microbial coatings and powders of biocompatible metals which provide a sustained release of
7 anti-microbial metal species when in contact with body fluids or body tissues.

8 **BACKGROUND OF THE INVENTION**

9 The need for an effective anti-microbial coating is well established in the
10 medical community. Physicians and surgeons using medical devices and appliances ranging
11 from orthopaedic pins, plates and implants through to wound dressings and urinary catheters
12 must constantly guard against infection. An inexpensive anti-microbial coating also finds
13 application in medical devices used in consumer healthcare and personal hygiene products as
14 well as in biomedical/biotechnical laboratory equipment. The term "medical device", as used
15 herein and in the claims is meant to extend to all such products.

16 The anti-microbial effects of metallic ions such as Ag, Au, Pt, Pd, Ir (i.e. the
17 noble metals), Cu, Sn, Sb, Bi and Zn are known (see Morton, H.E., Pseudomonas in
18 Disinfection, Sterilization and Preservation, ed. S.S. Block, Lea and Febiger, 1977 and Grier,
19 N., Silver and Its Compounds in Disinfection, Sterilization and Preservation, ed. S.S. Block,
20 Lea and Febiger, 1977). Of the metallic ions with anti-microbial properties, silver is perhaps
21 the best known due to its unusually good bioactivity at low concentrations. This phenomena
22 is termed oligodynamic action. In modern medical practice both inorganic and organic soluble
23 salts of silver are used to prevent and treat microbial infections. While these compounds are
24 effective as soluble salts, they do not provide prolonged protection due to loss through
25 removal or complexation of the free silver ions. They must be reapplied at frequent intervals
26 to overcome this problem. Reapplication is not always practical, especially where an in-
27 dwelling or implanted medical device is involved.

28 Attempts have been made to slow the release of silver ions during treatment by
29 creating silver containing complexes which have a lower level of solubility. For example,

1 U.S. Patent 2,785,153 discloses colloidal silver protein for this purpose. Such compounds are
2 usually formulated as creams. These compounds have not found wide applicability in the
3 medical area due to their limited efficacy. The silver ion release rate is very slow.
4 Furthermore, coatings from such compounds have been limited due to adhesion, abrasion
5 resistance and shelf life problems.

6 The use of silver metal coatings for anti-microbial purposes has been suggested.
7 For instance, see Deitch et al., Antimicrobial Agents and Chemotherapy, Vol. 23(3), 1983,
8 pp. 356 - 359 and Mackeen et al., Antimicrobial Agents and Chemotherapy, Vol. 31(1), 1987,
9 pp. 93 - 99. However, it is generally accepted that such coatings alone do not provide the
10 required level of efficacy, since diffusion of silver ions from the metallic surface is negligible.

11 A silver metal coating is produced by Spire Corporation, U.S.A. under the
12 trade mark SPI-ARGENT. The coating is formed by an ion-beam assisted deposition (IBAD)
13 coating process. The infection resistant coating is stated to be non-leaching in aqueous
14 solutions as demonstrated by zone of inhibition tests, thus enforcing the belief that silver metal
15 surfaces do not release anti-microbial amounts of silver ions.

16 Given the failure of metallic silver coatings to generate the required anti-
17 microbial efficacy, other researchers have tried novel activation processes. One technique is
18 to use electrical activation of metallic silver implants (see Marino et al., Journal of Biological
19 Physics, Vol. 12, 1984, pp. 93 - 98). Electrical stimulation of metallic silver is not always
20 practical, especially for mobile patients. Attempts to overcome this problem include
21 developing in situ electrical currents through galvanic action. Metal bands or layers of
22 different metals are deposited on a device as thin film coatings. A galvanic cell is created
23 when two metals in contact with each other are placed in an electrically conducting fluid. One
24 metal layer acts as an anode, which dissolves into the electrolyte. The second metal acts as
25 a cathode to drive the electrochemical cell. For example, in the case of alternating layers of
26 Cu and Ag, the Cu is the anode, releasing Cu^+ ions into the electrolyte. The more noble of
27 the metals, Ag, acts as the cathode, which does not ionize and does not go into solution to any
28 large extent. An exemplary device of this nature is described in U.S. Patent 4,886,505 issued
29 Dec. 12, 1989, to Haynes et al. The patent discloses sputtered coatings of two or more
30 different metals with a switch affixed to one of the metals such that, when the switch is
31 closed, metal ion release is achieved.

1 Previous work has shown that a film composed of thin laminates of alternating,
2 different metals such as silver and copper can be made to dissolve if the surface is first etched.
3 In this instance, the etching process creates a highly textured surface (see M. Tanemura and
4 F. Okuyama, J. Vac. Sci. Technol., 5, 1986, pp 2369-2372). However, the process of
5 making such multilaminated films is time consuming and expensive.

6 Electrical activation of metallic coatings has not presented a suitable solution
7 to the problem. It should be noted that galvanic action will occur only when an electrolyte
8 is present and if an electrical connection between the two metals of the galvanic couple exists.
9 Since galvanic corrosion occurs primarily at the metallic interface between the two metals,
10 electrical contact is not sustained. Thus a continuous release of metal ions over an extended
11 period of time is not probable. Also, galvanic action to release a metal such as silver is
12 difficult to achieve. As indicated above, the metal ions exhibiting the greatest anti-microbial
13 effect are the noble metals, such as Ag, Au, Pt and Pd. There are few metals more noble
14 than these to serve as cathode materials so as to drive the release of a noble metal such as Ag
15 at the anode.

16 A second approach to activating the silver metal surface is to use heat or
17 chemicals. U.S. Patents 4,476,590 and 4,615,705, issued to Scales et al. on October 16, 1984
18 and October 7, 1986, respectively, disclose methods of activating silver surface coatings on
19 endoprosthetic implants to render them bioerodible by heating at greater than 180°C or by
20 contacting with hydrogen peroxide. Such treatments are limited in terms of the
21 substrate/devices which can be coated and activated.

22 There is still a need for an efficacious, inexpensive anti-microbial material
23 having the following properties:

- 24 - sustained release of an anti-microbial agent at therapeutically active levels;
- 25 - applicable to a wide variety of devices and materials;
- 26 - useful shelf life; and
- 27 - low mammalian toxicity.

28 Metal coatings are typically produced as thin films by vapour deposition
29 techniques such as sputtering. Thin films of metals, alloys, semiconductors and ceramics are
30 widely used in the production of electronic components. These and other end uses require the
31 thin films to be produced as dense, crystalline structures with minimal defects. The films are
32 often annealed after deposition to enhance grain growth and recrystallization and produce

1 stable properties. Techniques to deposit metal films are reviewed by R.F. Bunshah et al.,
2 "Deposition Technologies for Films and Coatings", Noyes Publications, N.J., 1982 and by
3 J.A. Thornton, "Influence of Apparatus Geometry and Deposition Conditions on the Structure
4 and Topography of Thick Sputtered Coatings", J. Vac. Sci. Technol., 11(4), 666-670, 1974.

5 U.S. Patent No. 4,325,776, issued April 20, 1982 to Menzel discloses a process
6 for producing coarse or single crystal metal films from certain metals for use in integrated
7 circuits. The metal film is formed by depositing on a cooled substrate (below -90°C) such that
8 the metal layer is in an amorphous phase. The metal layer is then annealed by heating the
9 substrate up to about room temperature. The end product is stated to have large grain
10 diameter and great homogeneity, permitting higher current densities without electromigration
11 failures.

12 SUMMARY OF THE INVENTION

13 The inventors set out to develop an antimicrobial metal coating. They
14 discovered that, contrary to previous belief, it is possible to form metal coatings from an
15 antimicrobial metal material by creating atomic disorder in the materials by vapour deposition
16 under conditions which limit diffusion, that is which "freeze-in" the atomic disorder. The
17 anti-microbial coatings so produced were found to provide sustained release of anti-microbial
18 metal species into solution so as to produce an anti-microbial effect.

19 This basic discovery linking "atomic disorder" to enhanced solubility has broad
20 application. The inventors have demonstrated that atomic disorder so as to produce solubility
21 can be created in other material forms, such as metal powders. The invention also has
22 application beyond anti-microbial metals, encompassing any metal, metal alloy, or metal
23 compound, including semiconductor or ceramic materials, from which sustained release of
24 metal species into solution is desired. For instance, materials having enhanced or controlled
25 metal dissolution find application in sensors, switches, fuses, electrodes, and batteries.

26 The term "atomic disorder" as used herein includes high concentrations of:
27 point defects in a crystal lattice, vacancies, line defects such as dislocations, interstitial atoms,
28 amorphous regions, grain and sub grain boundaries and the like relative to its normal ordered
29 crystalline state. Atomic disorder leads to irregularities in surface topography and
30 inhomogenities in the structure on a nanometre scale.

1 By the term "normal ordered crystalline state" as used herein is meant the
2 crystallinity normally found in bulk metal materials, alloys or compounds formed as cast,
3 wrought or plated metal products. Such materials contain only low concentrations of such
4 atomic defects as vacancies, grain boundaries and dislocations.

5 The term "diffusion" as used herein implies diffusion of atoms and/or molecules
6 on the surface or in the matrix of the material being formed.

7 The terms "metal" or "metals" as used herein are meant to include one or more
8 metals whether in the form of substantially pure metals, alloys or compounds such as oxides,
9 nitrides, borides, sulphides, halides or hydrides.

10 The invention, in a broad aspect extends to a method of forming a modified
11 material containing one or more metals. The method comprises creating atomic disorder in
12 the material under conditions which limit diffusion such that sufficient atomic disorder is
13 retained in the material to provide release, preferably on a sustainable basis, of atoms, ions,
14 molecules or clusters of at least one of the metals into a solvent for the material. Clusters are
15 known to be small groups of atoms, ions or the like, as described by R.P. Andres et al.,
16 "Research Opportunities on Clusters and Cluster-Assembled Materials", J. Mater. Res. Vol.
17 4, No. 3, 1989, P. 704.

18 Specific preferred embodiments of the invention demonstrate that atomic
19 disorder may be created in metal powders or foils by cold working, and in metal coatings by
20 depositing by vapour deposition at low substrate temperatures.

21 In another broad aspect, the invention provides a modified material comprising
22 one or more metals in a form characterized by sufficient atomic disorder such that the
23 material, in contact with a solvent for the material, releases atoms, ions, molecules or clusters
24 containing at least one metal, preferably on a sustainable basis, at an enhanced rate relative
25 to its normal ordered crystalline state.

26 In preferred embodiments of the invention, the modified material is a metal
27 powder which has been mechanically worked or compressed, under cold working conditions,
28 to create and retain atomic disorder.

29 The term "metal powder" as used herein is meant to include metal particles of
30 a broad particle size, ranging from nanocrystalline powders to flakes.

31 The term "cold working" as used herein indicates that the material has been
32 mechanically worked such as by milling, grinding, hammering, mortar and pestle or

1 compressing, at temperatures lower than the recrystallization temperature of the material.
2 This ensures that atomic disorder imparted through working is retained in the material.

3 In another preferred embodiment, the modified material is a metal coating
4 formed on a substrate by vapour deposition techniques such as vacuum evaporation,
5 sputtering, magnetron sputtering or ion plating. The material is formed under conditions
6 which limit diffusion during deposition and which limit annealing or recrystallization following
7 deposition. The deposition conditions preferably used to produce atomic disorder in the
8 coatings are outside the normal range of operating conditions used to produce defect free,
9 dense, smooth films. Such normal practices are well known (see for example R.F. Bunshah
10 et al., supra). Preferably the deposition is conducted at low substrate temperatures such that
11 the ratio of the substrate to the melting point of the metal or metal compound being deposited
12 (T/T_m) is maintained at less than about 0.5, more preferably at less than about 0.35, and most
13 preferably at less than 0.30. In this ratio, the temperatures are in degrees Kelvin. The
14 preferred ratio will vary from metal to metal and increases with alloy or impurity content.
15 Other preferred deposition conditions to create atomic disorder include one or more of a
16 higher than normal working gas pressure, a lower than normal angle of incidence of the
17 coating flux and a higher than normal coating flux.

18 The temperature of deposition or cold working is not so low that substantial
19 annealing or recrystallization will take place when the material is brought to room temperature
20 or its intended temperature for use (ex. body temperature for anti-microbial materials). If the
21 temperature differential between deposition and temperature of use (ΔT) is too great, annealing
22 results, removing atomic disorder. This ΔT will vary from metal to metal and with the
23 deposition technique used. For example, with respect to silver, substrate temperatures of -20
24 to 200°C are preferred during physical vapour deposition.

25 Normal or ambient working gas pressure for depositing the usually required
26 dense, smooth, defect free metal films vary according to the method of physical vapour
27 deposition being used. In general, for sputtering, the normal working gas pressure is less than
28 75 mT (milliTorr), for magnetron sputtering, less than 10mT, and for ion-plating less than
29 200 mT. Normal ambient gas pressures vary for vacuum evaporation processes vary as
30 follows: for e-beam or arc evaporation, from 0.001 to 0.01 mT; for gas scattering
31 evaporation (pressure plating) and reactive arc evaporation, up to 200 mT, but typically less
32 than 20 mT. Thus, in accordance with the method of the present invention, in addition to

1 using low substrate temperatures to achieve atomic disorder, working (or ambient) gas
2 pressures higher than these normal values may be used to increase the level of atomic disorder
3 in the coating.

4 Another condition discovered to have an effect on the level of atomic disorder
5 in the coatings of the present invention is the angle of incidence of the coating flux during
6 deposition. Normally to achieve dense, smooth coatings, this angle is maintained at about 90°
7 $\pm 15^{\circ}$. In accordance with the present invention, in addition to using low substrate
8 temperatures during deposition to achieve atomic disorder, angles of incidence lower than
9 about 75° may be used to increase the level of atomic disorder in the coating.

10 Yet another process parameter having an effect on the level of atomic disorder
11 is the atom flux to the surface being coated. High deposition rates tend to increase atomic
12 disorder, however, high deposition rates also tend to increase the coating temperature. Thus,
13 there is an optimum deposition rate that depends on the deposition technique, the coating
14 material and other process parameters.

15 To provide an anti-microbial material, the metals used in the coating or powder
16 are those which have an anti-microbial effect, but which are biocompatible (non-toxic for the
17 intended utility). Preferred metals include Ag, Au, Pt, Pd, Ir (i.e. the noble metals), Sn, Cu,
18 Sb, Bi, and Zn, compounds of these metals or alloys containing one more of these metals.
19 Such metals are hereinafter referred to as "anti-microbial metals"). Most preferred is Ag or
20 its alloys and compounds. Anti-microbial materials in accordance with this invention
21 preferably are formed with sufficient atomic disorder that atoms, ions, molecules or clusters
22 of the anti-microbial material are released into an alcohol or water based electrolyte on a
23 sustainable basis. The terms "sustainable basis" is used herein to differentiate, on the one
24 hand from the release obtained from bulk metals, which release metal ions and the like at a
25 rate and concentration which is too low to achieve an anti-microbial effect, and on the other
26 hand from the release obtained from highly soluble salts such as silver nitrate, which release
27 silver ions virtually instantly in contact with an alcohol or water based electrolyte. In
28 contrast, the anti-microbial materials of the present invention release atoms, ions, molecules
29 or clusters of the anti-microbial metal at a sufficient rate and concentration, over a sufficient
30 time period to provide a useful anti-microbial effect.

31 The term "anti-microbial effect" as used herein means that atoms, ions,
32 molecules or clusters of the anti-microbial metal are released into the electrolyte which the

1 material contacts in concentrations sufficient to inhibit bacterial growth in the vicinity of the
2 material. The most common method of measuring anti-microbial effect is by measuring the
3 zone of inhibition (ZOI) created when the material is placed on a bacterial lawn. A relatively
4 small or no ZOI (ex. less than 1 mm) indicates a non-useful anti-microbial effect, while a
5 larger ZOI (ex. greater than 5 mm) indicates a highly useful anti-microbial effect. One
6 procedure for a ZOI test is set out in the Examples which follow.

7 The invention extends to devices such as medical devices formed from,
8 incorporating, carrying or coated with the anti-microbial powders or coatings. The anti-
9 microbial coating may be directly deposited by vapour deposition onto such medical devices
10 as catheters, sutures, implants, burn dressings and the like. An adhesion layer, such as
11 tantalum, may be applied between the device and the anti-microbial coating. Adhesion may
12 also be enhanced by methods known in the art, for example etching the substrate or forming
13 a mixed interface between the substrate and the coating by simultaneous sputtering and
14 etching. Anti-microbial powders may be incorporated into creams, polymers, ceramics,
15 paints, or other matrices, by techniques well known in the art.

16 In a further broad aspect of the invention, modified materials are prepared as
17 composite metal coatings containing atomic disorder. In this case, the coating of the one or
18 more metals or compounds to be released into solution constitutes a matrix containing atoms
19 or molecules of a different material. The presence of different atoms or molecules results in
20 atomic disorder in the metal matrix, for instance due to different sized atoms. The different
21 atoms or molecules may be one or more second metals, metal alloys or metal compounds
22 which are co- or sequentially deposited with the first metal or metals to be released.
23 Alternatively the different atoms or molecules may be absorbed or trapped from the working
24 gas atmosphere during reactive vapour deposition. The degree of atomic disorder, and thus
25 solubility, achieved by the inclusion of the different atoms or molecules varies, depending on
26 the materials. In order to retain and enhance the atomic disorder in the composite material,
27 one or more of the above-described vapour deposition conditions, namely low substrate
28 temperature, high working gas pressure, low angle of incidence and high coating flux, may
29 be used in combination with the inclusion of different atoms or molecules.

30 Preferred composite materials for anti-microbial purposes are formed by
31 including atoms or molecules containing oxygen, nitrogen, hydrogen, boron, sulphur or
32 halogens in the working gas atmosphere while depositing the anti-microbial metal. These

atoms or molecules are incorporated in the coating either by being absorbed or trapped in the film, or by reacting with the metal being deposited. Both of these mechanisms during deposition are hereinafter referred to as "reactive deposition". Gases containing these elements, for example oxygen, hydrogen, and water vapour, may be provided continuously or may be pulsed for sequential deposition.

Anti-microbial composite materials are also preferably prepared by co- or sequentially depositing an anti-microbial metal with one or more inert biocompatible metals selected from Ta, Ti, Nb, Zn, V, Hf, Mo, Si, and Al. Alternatively, the composite materials may be formed by co-, sequentially or reactively depositing one or more of the anti-microbial metals as the oxides, carbides, nitrides, borides, sulphides or halides of these metals and/or the oxides, carbides, nitrides, borides, sulphides or halides of the inert metals. Particularly preferred composites contain oxides of silver and/or gold, alone or together with one or more oxides of Ta, Ti, Zn and Nb.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

As above stated, the present invention has application beyond anti-microbial materials. However, the invention is disclosed herein with anti-microbial metals, which are illustrative of utility for other metals, metal alloys and metal compounds. Preferred metals include Al and Si, and the metal elements from the following groups of the periodic table: IIIB, IVB, VB, VIB, VIIB, VIIIB, IB, IIB, IIIA, IVA, and VA (excluding As) in the periods 4, 5 and 6, (see Periodic Table as published in Merck Index 10th Ed., 1983, Merck and Co. Inc., Rahway, N.J., Martha Windholz). Different metals will have varying degrees of solubility. However, the creation and retention of atomic disorder in accordance with this invention results in enhanced solubility (release) of the metal as ions, atoms, molecules or clusters into an appropriate solvent i.e. a solvent for the particular material, typically a polar solvent, over the solubility of the material in its normal ordered crystalline state.

The medical devices formed from, incorporating, carrying or coated with the anti-microbial material of this invention generally come into contact with an alcohol or water based electrolyte including a body fluid (for example blood, urine or saliva) or body tissue (for example skin, muscle or bone) for any period of time such that microorganism growth on the device surface is possible. The term "alcohol or water based electrolyte" also includes

1 alcohol or water based gels. In most cases the devices are medical devices such as catheters,
2 implants, tracheal tubes, orthopaedic pins, insulin pumps, wound closures, drains, dressings,
3 shunts, connectors, prosthetic devices, pacemaker leads, needles, surgical instruments, dental
4 prostheses, ventilator tubes and the like. However, it should be understood that the invention
5 is not limited to such devices and may extend to other devices useful in consumer healthcare,
6 such as sterile packaging, clothing and footwear, personal hygiene products such as diapers
7 and sanitary pads, in biomedical or biotechnical laboratory equipment, such as tables,
8 enclosures and wall coverings, and the like. The term "medical device" as used herein and
9 in the claims is intended to extend broadly to all such devices.

10 The device may be made of any suitable material, for example metals, including
11 steel, aluminum and its alloys, latex, nylon, silicone, polyester, glass, ceramic, paper, cloth
12 and other plastics and rubbers. For use as an in-dwelling medical device, the device will be
13 made of a bioinert material. The device may take on any shape dictated by its utility, ranging
14 from flat sheets to discs, rods and hollow tubes. The device may be rigid or flexible, a factor
15 again dictated by its intended use.

16 Anti-Microbial Coatings

17 The anti-microbial coating in accordance with this invention is deposited as a
18 thin metallic film on one or more surfaces of a medical device by vapour deposition
19 techniques. Physical vapour techniques, which are well known in the art, all deposit the metal
20 from the vapour, generally atom by atom, onto a substrate surface. The techniques include
21 vacuum or arc evaporation, sputtering, magnetron sputtering and ion plating. The deposition
22 is conducted in a manner to create atomic disorder in the coating as defined hereinabove.
23 Various conditions responsible for producing atomic disorder are useful. These conditions are
24 generally avoided in thin film deposition techniques where the object is to create a defect free,
25 smooth and dense film (see for example J.A. Thornton, supra). While such conditions have
26 been investigated in the art, they have not heretofore been linked to enhanced solubility of the
27 coatings so-produced.

28 The preferred conditions which are used to create atomic disorder during the
29 deposition process include:

30 - a low substrate temperature, that is maintaining the surface to be coated at a
31 temperature such that the ratio of the substrate temperature to the melting point of the metal

1 (in degrees Kelvin) is less than about 0.5, more preferably less than about 0.35 and most
2 preferably less than about 0.3; and optionally one or both of:

3 - a higher than normal working (or ambient) gas pressure, i.e. for vacuum
4 evaporation: e-beam or arc evaporation, greater than 0.01 mT, gas scattering evaporation
5 (pressure plating) or reactive arc evaporation, greater than 20 mT; for sputtering: greater than
6 75 mT; for magnetron sputtering: greater than about 10 mT; and for ion plating: greater than
7 about 200 mT; and

8 - maintaining the angle of incidence of the coating flux on the surface to be
9 coated at less than about 75°, and preferably less than about 30°

10 The metals used in the coating are those known to have an anti-microbial effect.
11 For most medical devices, the metal must also be biocompatible. Preferred metals include the
12 noble metals Ag, Au, Pt, Pd, and Ir as well as Sn, Cu, Sb, Bi, and Zn or alloys or
13 compounds of these metals or other metals. Most preferred is Ag or Au, or alloys or
14 compounds of one or more of these metals.

15 The coating is formed as a thin film on at least a part of the surface of the
16 medical device. The film has a thickness no greater than that needed to provide release of
17 metal ions on a sustainable basis over a suitable period of time. In that respect, the thickness
18 will vary with the particular metal in the coating (which varies the solubility and abrasion
19 resistance), and with the degree of atomic disorder in (and thus the solubility of) the coating.
20 The thickness will be thin enough that the coating does not interfere with the dimensional
21 tolerances or flexibility of the device for its intended utility. Typically, thicknesses of less
22 than 1 micron have been found to provide sufficient sustained anti-microbial activity.
23 Increased thicknesses may be used depending on the degree of metal ion release needed over
24 a period of time. Thicknesses greater than 10 microns are more expensive to produce and
25 normally should not be needed.

26 The anti-microbial effect of the coating is achieved when the device is brought
27 into contact with an alcohol or a water based electrolyte such as, a body fluid or body tissue,
28 thus releasing metal ions, atoms, molecules or clusters. The concentration of the metal which
29 is needed to produce an anti-microbial effect will vary from metal to metal. Generally, anti-
30 microbial effect is achieved in body fluids such as plasma, serum or urine at concentrations
31 less than about 0.5 - 1.5 $\mu\text{g/ml}$.

1 The ability to achieve release of metal atoms, ions, molecules or clusters on a
2 sustainable basis from a coating is dictated by a number of factors, including coating
3 characteristics such as composition, structure, solubility and thickness, and the nature of the
4 environment in which the device is used. As the level of atomic disorder is increased, the
5 amount of metal ions released per unit time increases. For instance, a silver metal film
6 deposited by magnetron sputtering at $T/T_m < 0.5$ and a working gas pressure of about 7
7 mTorr releases approximately 1/3 of the silver ions that a film deposited under similar
8 conditions, but at 30 mTorr, will release over 10 days. Films that are created with an
9 intermediate structure (ex. lower pressure, lower angle of incidence etc.) have Ag release
10 values intermediate to these values as determined by bioassays. This then provides a method
11 for producing controlled release metallic coatings in accordance with this invention. Slow
12 release coatings are prepared such that the degree of disorder is low while fast release coatings
13 are prepared such that the degree of disorder is high.

14 For continuous, uniform coatings, the time required for total dissolution will
15 be a function of film thickness and the nature of the environment to which they are exposed.
16 The relationship in respect of thickness is approximately linear, i.e. a two fold increase in film
17 thickness will result in about a two fold increase in longevity.

18 It is also possible to control the metal release from a coating by forming a thin
19 film coating with a modulated structure. For instance, a coating deposited by magnetron
20 sputtering such that the working gas pressure was low (ex. 15 mTorr) for 50% of the
21 deposition time and high (ex. 30 mTorr) for the remaining time, has a rapid initial release of
22 metal ions, followed by a longer period of slow release. This type of coating is extremely
23 effective on devices such as urinary catheters for which an initial rapid release is required to
24 achieve immediate anti-microbial concentrations followed by a lower release rate to sustain
25 the concentration of metal ions over a period of weeks.

26 The substrate temperature used during vapour deposition should not be so low
27 that annealing or recrystallization of the coating takes place as the coating warms to ambient
28 temperatures or the temperatures at which it is to be used (ex. body temperature). This
29 allowable ΔT , that the temperature differential between the substrate temperature during
30 deposition and the ultimate temperature of use, will vary from metal to metal. For the most
31 preferred metals of Ag and Au, preferred substrate temperatures of -20 to 200°C, more
32 preferably -10°C to 100°C are used.

1 Atomic order may also be achieved, in accordance with the present invention,
2 by preparing composite metal materials, that is materials which contain one or more anti-
3 microbial metals in a metal matrix which includes atoms or molecules different from the anti-
4 microbial metals.

5 Our technique for preparing composite material is to co- or sequentially deposit
6 the anti-microbial metal(s) with one or more other inert, biocompatible metals selected from
7 Ta, Ti, Nb, Zn, V, Hf, Mo, Si, Al and alloys of these metals or other metal elements,
8 typically other transition metals. Such inert metals have a different atomic radii from that of
9 the anti-microbial metals, which results in atomic disorder during deposition. Alloys of this
10 kind can also serve to reduce atomic diffusion and thus stabilize the disordered structure.
11 Thin film deposition equipment with multiple targets for the placement of each of the anti-
12 microbial and inert metals is preferably utilized. When layers are sequentially deposited the
13 layer(s) of the inert metal(s) should be discontinuous, for example as islands within the anti-
14 microbial metal matrix. The final ratio of the anti-microbial metal(s) to inert metal(s) should
15 be greater than about 0.2. The most preferable inert metals are Ti, Ta, Zn and Nb. It is also
16 possible to form the anti-microbial coating from oxides, carbides, nitrides, sulphides, borides,
17 halides or hydrides of one or more of the anti-microbial metals and/or one or more of the inert
18 metals to achieve the desired atomic disorder.

19 Another composite material within the scope of the present invention is formed
20 by reactively co- or sequentially depositing, by physical vapour techniques, a reacted material
21 into the thin film of the anti-microbial metal(s). The reacted material is an oxide, nitride,
22 carbide, boride, sulphide, hydride or halide of the anti-microbial and/or inert metal, formed
23 in situ by injecting the appropriate reactants, or gases containing same, (ex. air, oxygen,
24 water, nitrogen, hydrogen, boron, sulphur, halogens) into the deposition chamber. Atoms or
25 molecules of these gases may also become absorbed or trapped in the metal film to create
26 atomic disorder. The reactant may be continuously supplied during deposition for
27 codeposition or it may be pulsed to provide for sequential deposition. The final ratio of anti-
28 microbial metal(s) to reaction product should be greater than about 0.2. Air, oxygen, nitrogen
29 and hydrogen are particularly preferred reactants.

30 The above deposition techniques to prepare composite coatings may be used
31 with or without the conditions of lower substrate temperatures, high working gas pressures and

1 low angles of incidence previously discussed. One or more of these conditions is preferred
2 to retain and enhance the amount of atomic disorder created in the coating.

3 It may be advantageous, prior to depositing an anti-microbial in accordance with
4 the present invention, to provide an adhesion layer on the device to be coated, as is known
5 in the art. For instance, for a latex device, a layer of Ti, Ta or Nb may be first deposited to
6 enhance adhesion of the subsequently deposited anti-microbial coating.

7 Anti-Microbial Powders

8 Anti-microbial powders, including nanocrystalline powders and powders made
9 from rapidly solidified flakes or foils, can be formed with atomic disorder so as to enhance
10 solubility. The powders either as pure metals, metal alloys or compounds such as metal
11 oxides or metal salts, can be mechanically worked or compressed to impart atomic disorder.
12 This mechanically imparted disorder is conducted under conditions of low temperature (i.e.
13 temperatures less than the temperature of recrystallization of the material) to ensure that
14 annealing or recrystallization does not take place. The temperature varies between metals and
15 increases with alloy or impurity content.

16 Anti-microbial powders produced in accordance with this invention may be used
17 in a variety of forms, for instance in topical creams, paints or adherent coatings.
18 Alternatively, the powder may be incorporated into a polymeric, ceramic or metallic matrix
19 to be used as a material for medical devices or coatings therefor.

20 The invention is further illustrated by the following non-limiting examples.

21 Example 1

22 A medical suture material size 2/0, polyester braid was coated by magnetron
23 sputtering an Ag-Cu-alloy onto the surface to a thickness of 0.45 microns, using either argon
24 gas working pressures of 7 mTorr or 30 mT at 0.5 KW power and a T/T_m ratio of less than
25 0.5.

26 The anti-microbial effect of the coatings was tested by a zone of inhibition test.
27 Basal medium Eagle (BME) with Earle's salts and L-glutamine was modified with calf/serum
28 (10%) and 1.5 % agar prior to being dispensed (15 ml) into Petri dishes. The agar
29 containing Petri plates were allowed to surface dry prior to being inoculated with a lawn of

1 *Staphylococcus aureus* ATCC# 25923. The inoculant was prepared from Bactrol Discs
2 (Difco, M.) which were reconstituted as per the manufacturer's directions. Immediately after
3 inoculation, the materials or coatings to be tested were placed on the surface of the agar. The
4 dishes were incubated for 24 h at 37°C. After this incubation period, the zone of inhibition
5 was measured and a corrected zone of inhibition was calculated (corrected zone of inhibition
6 = zone of inhibition - diameter of the test material in contact with the agar).

7 The results showed no zone of inhibition on the uncoated suture, a zone of less
8 than 0.5 mm around the suture coated at 7 mTorr and a zone of 13 mm around the suture
9 coated at 30 mTorr. Clearly the suture coated in accordance with the present invention
10 exhibits a much more pronounced and effective anti-microbial effect.

11 Example 2

12 This example is included to illustrate the surface structures which are obtained
13 when silver metal is deposited on silicon wafers using a magnetron sputtering facility and
14 different working gas pressures and angles of incidence (i.e. the angle between the path of the
15 sputtered atoms and the substrate). All other conditions were as follows: deposition rate was
16 200 Å/min; ratio of temperature of substrate (wafer) to melting point of silver (1234°K),
17 T/T_m was less than 0.3. Argon gas pressures of 7 mTorr (a normal working pressure for
18 metal coatings) and 30 mTorr were used. Angles of incidence at each of these pressures were
19 90° (normal incidence), 50° and 10°. The coatings had a thickness of about 0.5 microns.

20 The resulting surfaces were viewed by scanning electron microscope. As argon
21 gas pressure increased from 7 to 30 mTorr the grain size decreased and void volume increased
22 significantly. When the angle of incidence was decreased, the grain size decreased and the
23 grain boundaries became more distinct. At 7 mTorr argon pressure and an angle of incidence
24 of 10°, there were indications of some voids between the grains. The angle of incidence had
25 a greater effect on the surface topography when the gas pressure was increased to 30 mTorr.
26 At 90°, the grain size varied from 60 - 150 nm and many of the grains were separated by
27 intergrain void spaces which were 15 - 30 nm wide. When the angle of incidence was
28 decreased to 50°, the grain size decreased to 30 - 90 nm and the void volume increased
29 substantially. At 10°, the grain size was reduced to about 10 - 60 nm and void volumes were
30 increased again.

1 The observed nanometre scale changes in surface morphology and topography
2 are indications of atomic disorder in the silver metal. While not being bound by the same,
3 it is believed that such atomic disorder results in an increase in the chemical activity due to
4 increased internal stresses and surface roughness created by mismatched atoms. It is believed
5 that the increased chemical activity is responsible for the increased level of solubility of the
6 coatings when in contact with an electrolyte such as body fluid.

7 The anti-microbial effect of the coatings was evaluated using the zone of
8 inhibition test as set out in Example 1. Each coated silicon wafer was placed on an individual
9 plate. The results were compared to the zones of inhibition achieved when solid silver (i.e.
10 greater than 99% silver) sheets, wires or membranes were tested. The results are summarized
11 in Table 1. It is evident that the pure silver devices and the silver sputtered coating at 7
12 mTorr do not produce any biological effect. However, the coatings deposited at a higher than
13 normal working gas pressure, 30 mTorr, demonstrated an anti-microbial effect, as denoted by
14 the substantial zones of inhibition around the discs. Decreasing the angle of incidence had the
15 greatest effect on anti-microbial activity when combined with the higher gas pressures.

Table 1

Antimicrobial effects of various silver and silver coated samples as determined using *Staphylococcus aureus*

Sample	Percent Silver	Angle of Deposition	Working Gas Pressure (mTorr)	Corrected Zone of Inhibition (mm)
Silver Sheet-rolled	99+	-	-	<0.5
Silver wire (.0045")	99+	-	-	<0.5
Silver membrane-cast	99+	-	-	<0.5
Sputtered thin film	99+	normal (90°)	7	<0.5
Sputtered thin film	99+	50°	7	<0.5
Sputtered thin film	99+	10°	7	<0.5
Sputtered thin film	99+	normal (90°)	30	6.3
Sputtered thin film	99+	50°	30	10
Sputtered thin film	99+	10	30	10

Example 3

Silicon wafers were coated by magnetron sputtering with an alloy of Ag and Cu (80:20) at normal incidence at working gas pressures of 7 mTorr and 30 mTorr, all other conditions being identical to those set out in Example 2. As in Example 2, when the coatings were viewed by SEM, the coatings formed at high working gas pressure had smaller grain sizes and larger void volumes than did the coatings formed at the lower working gas pressures.

Coatings which were similarly formed from a 50:50 Ag/Cu alloy were tested for anti-microbial activity with the zone of inhibition test set out in Example 1. The results are summarized in Table 2. Coatings deposited at low working gas pressure (7 mTorr) showed minimal zones of inhibition, while the coatings deposited at high working gas pressure (30 mTorr) produced larger zones of inhibition, indicative of anti-microbial activity.

Table 2
The antimicrobial effect of various sputter deposited silver-copper alloys as determined using *Staphylococcus aureus*

Sample	Percent Silver	Angle of Deposition (°)	Working Gas Pressure (mTorr)	Corrected Zone of Inhibition (mm)
1	50	normal (90°)	7.5	<0.5
2	50	normal (90°)	30	16
3	50	10	30	19

1 **Example 4**

2 A coating in accordance with the present invention was tested to determine the
3 concentration of silver ions released into solution over time. One cm² silicon wafer discs were
4 coated with silver as set forth in Example 2 at 7 mTorr and 30 mTorr and normal incidence
5 to a thickness of 5000 Å. Using the method of Nickel et al., Eur. J. Clin. Microbiol., 4(2),
6 213-218, 1985, a sterile synthetic urine was prepared and dispensed into test tubes (3.5 ml).
7 The coated discs were placed into each test tubes and incubated for various times at 37°C.
8 After various periods of time, the discs were removed and the Ag content of the filtered
9 synthetic urine was determined using neutron activation analysis.

10 The results are set forth in Table 3. The table shows the comparative amounts
11 of Ag released over time from coatings deposited on discs at 7 mTorr or 30 mTorr. The
12 coatings deposited at high pressure were more soluble than those deposited at low pressure.
13 It should be noted that this test is a static test. Thus, silver levels build up over time, which
14 would not be the case in body fluid where there is constant turn over.

Table 3

Concentration of silver in synthetic urine as a function of exposure time

Silver Concentration $\mu\text{g/ml}$

Exposure Time (Days)	Working Argon gas pressure 7mTorr	Working argon gas pressure 30mTorr
0	ND1	ND
1	0.89	1.94
3	1.89	2.36
10	8.14	23.06

Note: Films were deposited at normal incidence (90°)1 - ND (non detectable) $<0.46 \mu\text{g/ml}$

1 Example 5

2 This example is included to illustrate coatings in accordance with the present
3 invention formed from another noble metal, Pd. The coatings were formed on silicon wafers
4 as set forth in Example 2, to a thickness of 5000 Å, using 7 mTorr or 30 mTorr working
5 gas pressures and angles of incidence of 90° and 10°. The coated discs were evaluated for
6 anti-microbial activity by the zone of inhibition test substantially as set forth in Example 1.
7 The coated discs were placed coating side up such that the agar formed a 1 mm surface
8 coating over the discs. The medium was allowed to solidify and surface dry, after which the
9 bacterial lawn was spread over the surface. The dishes were incubated at 37°C for 24 h. The
10 amount of growth was then visually analyzed.

11 The results are set forth in Table 4. At high working gas pressures, the
12 biological activity of the coating was much greater than that of coatings deposited at low
13 pressure. Changing the angle of incidence (decreasing) improved the anti-microbial effect of
14 the coating to a greater extent when the gas pressure was low than when it was high.

Table 4

Surface Control of Staphylococcus aureus by Sputter Deposited Palladium metal

Sample	Sputtering Pressure	Angle of Deposition	Antimicrobial Control
1	7mT	90°(normal incidence)	More than 90% of surface covered by bacterial growth
2	7mT	10°(grazing incidence)	20-40% of surface covered by bacterial growth
3	30mT	90°(normal incidence)	Less than 10% surface covered by bacterial growth

Example 6

This example is included to illustrate the effect of silver deposition temperature on the antimicrobial activity of the coating. Silver metal was deposited on 2.5 cm sections of a latex Foley catheter using a magnetron sputtering facility. Operating conditions were as follows; the deposition rate was 200 Å⁰ per minute; the argon working gas pressure was 30mTorr; and the ratio of temperature of substrate to melting point of the coating metal silver, T/T_m was 0.30 or 0.38. In this example the angles of incidence were variable since the substrate was round and rough. That is the angles of incidence varied around the circumference and, on a finer scale, across the sides and tops of the numerous surface features. The antimicrobial effect was tested by a zone of inhibition test as outlined in Example 1.

The results showed corrected zones of inhibition of 0.5 and 16 mm around the tubing coated at T/T_m values of 0.38 and 0.30 respectively. The sections of Foley catheter coated at the lower T/T_m value were more efficacious than those coated at higher T/T_m value.

1 Example 7

2 This example is included to demonstrate an antimicrobial coating formed by DC
 3 magnetron sputtering on a commercial catheter. A teflon coated latex Foley catheter was
 4 coated by DC magnetron sputtering 99.99% pure silver on the surface using the conditions
 5 listed in Table 5. The working gases used were commercial Ar and 99/1 wt% Ar/O₂.

6 The antimicrobial effect of the coating was tested by a zone of inhibition test. Mueller
 7 Hinton agar was dispensed into Petri dishes. The agar plates were allowed to surface dry
 8 prior to being inoculated with a lawn of *Staphylococcus aureus* ATCC# 25923. The inoculant
 9 was prepared from Bactrol Discs (Difco, M.) which were reconstituted as per the
 10 manufacturer's directions. Immediately after inoculation, the coated materials to be tested
 11 were placed on the surface of the agar. The dishes were incubated for 24 hr. at 37°C. After
 12 this incubation period, the zone of inhibition was measured and a corrected zone of inhibition
 13 was calculated (corrected zone of inhibition = zone of inhibition - diameter of the test
 14 material in contact with the agar).

15 The results showed no zone of inhibition for the uncoated samples and a corrected zone
 16 of less than 1 mm for catheters sputtered in commercial argon at a working gas pressure of
 17 5 mT. A corrected zone of inhibition of 11 mm was reported for the catheters sputtered in
 18 the 99/1 wt% Ar/O₂ using a working gas pressure of 40 mT. XRD analysis showed that the
 19 coating sputtered in 1% oxygen was a crystalline Ag film. This structure clearly caused an
 20 improved anti-microbial effect for the coated catheters.

21 Table 5. Conditions of DC Magnetron Sputtering Used for Anti-Microbial Coatings

22	Samples Sputtered in Commercial Argon	Samples Sputtered in 99/1 wt% Ar/O ₂
23	Power 0.1 kW	Power 0.5 kW
24		
25		

1	Argon Pressure: 5 m Torr	Ar/O ₂ Pressure: 40 m Torr
2	Initial Substrate Temperature: 20°C	Initial Substrate Temperature: 20°C
3	Cathode/Anode Distance: 40 mm	Cathode/Anode Distance: 100mm
4	Film Thickness: 2500 A	Film Thickness: 3000 A
5	<hr/>	

6 Example 8

7 This example demonstrates silver coatings formed by arc evaporation, gas scattering
8 evaporation (pressure plating) and reactive arc evaporation. Evaporation of 99.99 % silver was
9 performed onto silicon or alumina wafers at an initial substrate temperature of about 21°C,
10 using the parameters as follows:

11 Bias: -100 V

12 Current: 20 Amp-hrs

13 Angle of incidence: 90°

14 Working Gas Pressure: 0.01 mT (arc), 26 mT Ar/H₂ 96:4 (gas scattering evaporation), and
15 26 mT O₂ (reactive arc evaporation)

16 No corrected ZOI was observed for wafers coated at vacuum (arc). Pressure plating
17 with a working gas atmosphere containing Ar and 4 % hydrogen produced a 6 mm ZOI, while
18 a working gas atmosphere of pure oxygen (reactive arc) produced an 8 mm ZOI. Film
19 thicknesses of about 4000 Angstroms were produced. The results indicate that the presence
20 of gases such as hydrogen and/or oxygen in the arc evaporation atmosphere cause the coatings
21 to have improved anti-microbial efficacy.

1 Example 9

2 This example is included to illustrate composite materials to produce anti-
3 microbial effects. A set of coatings were produced by RF magnetron sputtering zinc oxide
4 onto silicon wafers as outlined below. The zinc oxide coatings showed no zone of inhibition.

5 Coatings of Ag and ZnO were deposited to a total thickness of 3300 Angstroms
6 by sequentially sputtering layers of Ag with layers of ZnO, according to the conditions below,
7 in a 75/25 wt% ratio. The coatings were demonstrated to have no zone of inhibition when
8 the zinc oxide layers were about 100 Angstroms thick. However, films consisting of islands
9 of very thin to discontinuous layers of ZnO (less than 50 Angstroms) in an Ag matrix (ie. a
10 composite film) had a 8 mm corrected zone of inhibition.

11 The conditions used to deposit ZnO were as follows: Working gas = argon;
12 Working gas pressure = 30 mT; Cathode-Anode distance: 40 mm; Initial Substrate
13 Temperature: 21°C; Power: RF magnetron, 0.5 kW.

14 The conditions used to deposit the Ag were as follows:
15 Working gas = argon; Working gas pressure = 30 mT; Cathode-Anode distance = 40 mm;
16 Initial Substrate Temperature = 21°C; Power = DC magnetron, 0.1 kW.

17 Example 10

18 This example demonstrates the effects of cold working and annealing silver and
19 gold powders on the antimicrobial efficacy demonstrated by a standard zone of inhibition test.
20 Cold working of such powders results in a defective surface structure containing atomic
21 disorder which favours the release of ions causing antimicrobial activity. The antimicrobial
22 effect of this defective structure can be removed by annealing.

1 Nanocrystalline silver powder (crystal size about 30 nm) was sprinkled onto
2 adhesive tape and tested. A zone of inhibition of 5 mm was obtained, using the method set
3 forth in Example 7. A 0.3g pellet of the nanocrystalline Ag powder was pressed at 40,000
4 psi. The pellet produced a 9 mm zone of inhibition when tested for antimicrobial activity.
5 Nanocrystalline silver powder was mechanically worked in a ball mill for 30 sec. The
6 resulting powder was tested for antimicrobial activity, both by sprinkling the worked powder
7 on adhesive tape and applying to the plates, and by pressing the powder into a pellet at the
8 above conditions and placing the pellet on the plates. The zones of inhibition observed were
9 7 and 11 mm respectively. A pellet that had been pressed from the worked powder was
10 annealed at 500°C for 1 hour under vacuum conditions. A reduced zone of inhibition of 3 mm
11 was observed for the annealed pellet.

12 These results demonstrate that nanocrystalline silver powder, while having a
13 small anti-microbial effect on its own, has an improved antimicrobial effect by introducing
14 atomic disorder by mechanical working of the powder in a ball mill or by pressing it into a
15 pellet. The antimicrobial effect was significantly decreased by annealing at 500°C. Thus,
16 conditions of mechanical working should not include or be followed by conditions such as high
17 temperature, which allow diffusion. Cold mechanical working conditions are preferred to
18 limit diffusion, for example by working at room temperature or by grinding or milling in
19 liquid nitrogen.

20 Silver powder, 1 micron particle size, was tested in a manner similar to above.
21 The Ag powder sprinkled onto adhesive tape and tested for a zone of inhibition. No zone of
22 inhibition was observed. The powder was worked in a ball mill for 30 seconds and sprinkled
23 onto adhesive tape. A 6 mm zone of inhibition was observed around the powder on the tape.
24 When the Ag powder (as is or after mechanical working in the ball mill) was pressed into a

1 0.3 g pellet using 40,000 psi, zones of inhibition of 5 and 6 mm respectively were observed.
2 A pellet which was formed from the ball milled powder and which was annealed at 500°C for
3 1 hour had significantly reduced antimicrobial activity. Initially the pellet had some activity
4 (4.5 mm zone of inhibition) but after the pellet was tested a second time, no zone of inhibition
5 was observed. A control pellet which had not been annealed continued to give a zone of
6 inhibition greater than 4 mm even after 14 repeats of the test. This demonstrates that an
7 annealing step, following by mechanical working, limits the sustainable release of the
8 antimicrobial silver species from the powders.

9 Nanocrystalline gold (20 nm crystals), supplied as a powder, was tested for anti-
10 microbial effect by sprinkling the powder onto adhesive tape and using the zone of inhibition
11 test. No zone of inhibition was recorded for the nanocrystalline gold powder. The gold
12 powder was pressed into a 0.2 g pellet using 40,000 psi. A 10 mm zone of inhibition was
13 observed. When the pressed pellets were subsequently vacuum annealed at 500°C for 1 hour
14 and the zone of inhibition was found to be 0 mm.

15 The results showed that solubility and thus the anti-microbial efficacy of gold
16 powders can be improved by a mechanical working process such as pressing a nanocrystalline
17 material into a pellet. The antimicrobial activity can be removed by annealing. Cold working
18 is preferred.

19 Other gold powders including a 2-5 micron and a 250 micron particle size
20 powder did not demonstrate an antimicrobial effect under the above mechanical working
21 conditions. It is believed that the small grain size of the nanocrystalline gold powder was an
22 important cofactor which, with the mechanical working, produced the desired antimicrobial
23 effect.

1 Example 11

2 This example is included to demonstrate a composite antimicrobial coating
3 formed by reactive sputtering (another example of composite films). Example 7 demonstrates
4 that an antimicrobial coating of silver can be obtained by sputtering in argon and 1% oxygen
5 (0.5 kW, 40 mTorr, 100 mm anode/cathode distance, and 20°C - produced a zone of inhibition
6 of 11 mm).

7 When a working gas of argon and 20 wt% oxygen was used to sputter
8 antimicrobial coatings under the conditions listed below, the zones of inhibition ranged from
9 6 to 12 mm. This indicates that the provision of a reactive atmosphere during vapour
10 deposition has the result of producing an antimicrobial film over a wide range of deposition
11 process parameters.

12 Sputtering Conditions

13	Target	99.99% Ag
14	Working Gas:	80/20 wt% Ar/O ₂
15	Working Gas Pressure:	2.5 to 50 mTorr
16	Power:	0.1 to 2.5 kW
17	Substrate Temperature:	-5 to 20°C
18	Anode/Cathode Distance	40 to 100 mm
19	Base Pressure:	less than 4 x 10 ⁻⁶ Torr

20 Example 12

21 This example demonstrates that the coatings of this invention have an
22 antimicrobial effect against a broad spectrum of bacteria.

23 A total of 171 different bacterial samples encompassing 18 genera and 55
24 species were provide by the Provincial Laboratory of Public Health for Northern Alberta.
25 These samples had been quick frozen in 20% skim milk and stored at -70°C for periods

1 ranging from several months to several years. Fastidious organisms which were unlikely to
2 grow under conditions used in standard Kirby-Bauer susceptibility testing were not used.

3 Each frozen sample was scraped with a sterile cotton swab to inoculate a blood
4 agar plate (BAP). The plates were incubated overnight at 35°C. The following morning
5 isolated colonies were subcultured onto fresh BAPs and incubated at 35°C overnight. The next
6 day, the organisms were subjected to Kirby-Bauer susceptibility testing as described below.

7 Four to five colonies (more if colonies were small) of the same morphological
8 type were selected from each BAP subculture and inoculated into individual tubes containing
9 approximately 5 mL of tryptic soy broth (TSB). The broths were incubated at 35°C for
10 approximately 2 to 3 hours. At this time, the turbidity of most of the broth cultures either
11 equalled or exceeded that of a 0.5 McFarland standard. The more turbid samples were diluted
12 with sterile saline to obtain a turbidity visually comparable to that of the standard. To aid in
13 the visual assessment of turbidity, tubes were read against a white background with contrasting
14 black line.

15 A small number of the organisms (*Streptococcus* and *Corynebacterium*) did not
16 grow well in TSB. The turbidity of these broths, after incubation, was less than that of the
17 0.5 McFarland standard. Additional colonies from the BAP subcultures were inoculated to
18 these tubes to increase the turbidity to approximate that of the standard.

19 Within 15 minutes of adjusting the turbidity of the bacterial suspensions a sterile
20 cotton swab was dipped into each broth. Excess fluid was removed by rotating the swab
21 against the rim of the tube. The inoculum was applied to a Mueller Hinton (MH) agar plate
22 by streaking the swab evenly in three directions over the entire agar surface. Three 1 cm x
23 1 cm silver coated silica wafer squares were applied to each MH plate and the plates were
24 inverted and incubated overnight at 35°C. The coatings had been sputtered under the

1 following conditions, which through XFD analysis were shown to be silver/silver oxide
2 composite films:

3	Target:	99.99% Ag
4	Working gas:	Ar/O ₂ 80/20
5	Working gas pressure:	40 mT
6	Power:	0.1 kW
7	Temperature of Deposition	20°C
8	Base pressure	2 x 10 ⁻⁶ Torr
9	Cathode/anode distance	40 mm

10 BAP cultures of control organisms were provided by the Provincial Laboratory
11 and included: *Staphylococcus aureus* ATCC 25923; *Pseudomonas aeruginosa* ATCC 27853;
12 *Escherichia coli*: ATCC 25922; and *Enterococcus faecalis* ATCC 29212 to check the quality
13 of the MH agar. These cultures were treated in a like manner to the test organisms except
14 that standard antibiotic discs rather than silver coated wafers were applied to the bacterial
15 lawns on the MH agar. These organisms demonstrated that the MH agar was suitable for
16 standard ZOI tests.

17 After 16 to 18 hours of incubation at 35°C zones of inhibition around the silver
18 wafers or antibiotic discs were measured to the nearest mm. Corrected zones were calculated
19 by subtracting the size of the wafer (1 cm) from the size of the total zone. Representative
20 zone of inhibition results are shown in Table 7.

Table 7: The Sensitivity of a Broad Range of Microorganisms to Silver* Coated Silicon Wafers

Organism	Source	Corrected Zone of Inhibition (mm)
<i>Staphylococcus epidermidis</i> RC-455	blood	10
<i>Bacillus licheniformis</i> R-2138	tibia	6
<i>Corynebacterium sp</i> R-594	leg	10
<i>Listeria monocytogenes</i> R-590	blood	5
<i>Enterococcus faecalis</i> SR-113	bone	5
<i>Streptococcus bovis</i> SR-62	blood	10
<i>Escherichia coli</i> R-1878	urine	11
<i>Klebsiella ozonae</i> R-308/90	abdomen	10
<i>Enterobacter cloacae</i> R-1682	unknown	8
<i>Proteus vulgaris</i> 3781	urine	4
<i>Providencia stuartii</i> U-3179	urine	8
<i>Citrobacter freundii</i> U-3122/90	urine	7
<i>Salmonella typhimurium</i> ER-1154	urine	6
<i>Serratia marcescens</i> R-850	sputum	6
<i>Pseudomonas aeruginosa</i> U-3027	urine	10
<i>Xanthomonas maltophilia</i> 90-10B	unknown	9
<i>Aeromonas caviae</i> R-1211	wound	5
<i>Branhamella catarrhalis</i> R-2681	unknown	12
Silver deposition*		

1 **Example 13**

2 This example demonstrates the use of tantalum as an adhesive layer for coatings
3 of this invention. Tantalum is well known as a material which, in the form of an interlayer,
4 improves adhesion of thin films to substrates. In this example test sections including a group
5 of stainless steel (316) (1 x 1 cm) and silicon (1.7 X 0.9 cm) coupons and sections of latex
6 tubing (5 cm) were cleaned in ethanol and then half of the test sections were coated (by
7 sputtering) with a thin layer (approx. 100 Angstroms) of Ta before an antimicrobial silver film
8 was deposited on them. The second group of the test sections were only coated with the
9 antimicrobial Ag film. Coating conditions are listed below. While all test sections had similar
10 antimicrobial activity, the Ta coated test sections had much better adhesion properties than did
11 the untreated test sections. Adhesion properties were determined using ASTM method D3359-
12 87, a standard test method for measuring adhesion.

13 **Sputtering Conditions**

14	Target:	99.99% Ta
15	Working Gas:	99/1 wt% Ar/O ₂
16	Working Gas Pressure:	10 mTorr
17	Power:	0.5 kW
18	Cathode/Anode Distance:	100 mm
19	Substrate Temperature:	20°C
20	Target:	99.99% Ag
21	Working Gas:	99/1 wt% Ar/O ₂
22	Working Gas Pressure:	40 mTorr
23	Power:	0.5 kW
24	Cathode/Anode Distance:	100 mm
25	Substrate Temperature:	20°C

26 **Example 14**

27 DC magnetron sputtering was used to deposit silver from a 99.98% pure
28 cathode onto silicon and alumina wafers with commercial argon moisturized with water as the
29 working gas. The argon was moisturized by passing it through two flasks containing 3 litres

of room temperature water and one empty flask set up with glass wool to absorb any free liquid before the gas entered the sputtering unit.

The conditions of sputtering and the results of the standard zone of inhibition test performed on the sputtered silver films are shown below. Silver films which normally had no antimicrobial properties when deposited using argon that had not been treated with water yielded a corrected zone of inhibition of up to 8 mm when sputtered using a argon/water vapour mixture as the working gas.

Table 8: Conditions used for DC Magnetron Sputtering of Anti-Microbial Coatings

Working Gas	Working Gas Pressure	Power	Substrate Temperature	Anode/Cathode Distance	Corrected ZOI
Commercial Argon	10mTorr	0.5kW	-10°C	100 mm	0 mm
Ar passed through H ₂ O	10mTorr	0.5kW	-10°C	100 mm	8 mm

All publications mentioned in this specification are indicative of the level of skill of those skilled in the art to which this invention pertains. All publications are herein incorporated by reference to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference.

The terms and expressions in this specification are used as terms of description and not of limitation. There is no intention, in using such terms and expressions, of excluding equivalents of the features illustrated and described, it being recognized that the scope of the invention is defined and limited only by the claims which follow.

1 Claims

2 1. A modified material comprising:

3 one or more metals in a form characterized by sufficient atomic disorder such
4 that the material, in contact with a solvent for the material, releases atoms, ions, molecules
5 or clusters containing at least one metal at an enhanced rate relative to its normal ordered
6 crystalline state.

7 2. The material as set forth in claim 1 in the form of a powder or foil.

8 3. The material as set forth in claim 1 in the form of a coating.

9 4. The material as set forth in claim 2, wherein the material is cold worked to
10 create the atomic disorder.11 5. The material as set forth in claim 3, wherein the material is formed by vapour
12 deposition.13 6. The material as set forth in claim 5, wherein the material is formed by physical
14 vapour deposition.15 7. The material as set forth in claim 1, 2 or 3, wherein at least one of the metals
16 is an anti-microbial metal and wherein the material is formed with sufficient atomic disorder
17 that the atoms, ions, molecules or clusters of the anti-microbial metal are released on a
18 sustainable basis.19 8. The material as set forth in claim 1, 4, or 6, wherein the metal is selected from
20 the group consisting of Ag, Au, Pt, Pd, Ir, Sn, Cu, Sb, Bi, and Zn or an alloy or compound
21 thereof.22 9. The material as set forth in claim 1, 4, or 6, wherein the metal is Ag, Au or
23 Pd or an alloy or compound of one or more of these metals.

1 10. A method of forming a modified material containing one or more metals, said
2 method comprising:

3 creating atomic disorder in the material under conditions which limit diffusion
4 such that sufficient atomic disorder is retained in the material to provide release of atoms,
5 ions, molecules or clusters of at least one of the metals into a solvent for the material at an
6 enhanced rate relative to its normal ordered crystalline state.

7 11. The method as set forth in claim 10 wherein the material is a powder or foil
8 of one or more of the metals, and wherein the atomic disorder is formed by cold working of
9 the powder or foil.

10 12. The method as set forth in claim 11, wherein the powder or foil is worked at
11 a temperature below the recrystallization temperature for the powder or foil to retain atomic
12 disorder.

13 13. The method as set forth in claim 12, wherein the material is a nanocrystalline
14 powder.

15 14. The method as set forth in claim 12, wherein at least one of the metals is an
16 anti-microbial metal and wherein the material is formed with sufficient atomic disorder that
17 atoms, ions, molecules or clusters of the anti-microbial metal are released on a sustainable
18 basis.

19 15. The method as set forth in claim 12, wherein at least one of the metals is
20 selected from the group consisting of Ag, Au, Pt, Pd, Ir, Sn, Cu, Sb, Bi and Zn or alloys or
21 compounds of one or more of these metals.

22 16. The method as set forth in claim 12, wherein at least one of the metals is Ag,
23 Au or Pd or an alloy or compound containing one or more of these metals.

1 17. The method as set forth in claim 12, wherein at least one of the metals is silver
2 or an alloy or compound containing silver.

3 18. The method as set forth in claim 10, wherein the material is formed as a coating
4 on a substrate by vapour deposition under conditions which limit diffusion during deposition
5 and which limit annealing or recrystallization following deposition.

6 19. The method as set forth in claim 18, wherein the material is formed by physical
7 vapour deposition.

8 20. The method as set forth in claim 19, wherein the material is a coating of one
9 or more of the metals formed on a substrate by vacuum evaporation, sputtering, magnetron
10 sputtering or ion plating.

11 21. The method as set forth in claim 20, wherein the deposition is performed under
12 conditions such that the ratio of the temperature of the substrate to the melting point of the
13 metal or metal compound being deposited is maintained at less than about 0.5.

14 22. The method as set forth in claim 21 wherein the ratio is maintained at less than
15 about 0.3.

16 23. The method as set forth in claim 21, wherein the deposition is performed such
17 that the angle of incidence of the coating flux on the substrate to be coated is less than about
18 75°.

19 24. The method as set forth in claim 21, wherein the deposition is performed by
20 arc evaporation at an ambient or working gas pressure of greater than about 0.01 mT.

21 25. The method as set forth in claim 21, wherein the deposition is performed by
22 gas scattering evaporation at a working gas pressure of greater than about 20 mT.

23 26. The method as set forth in claim 21, wherein the deposition is performed by
24 sputtering at a working gas pressure of greater than about 75 mT.

1 27. The method as set forth in claim 21, wherein the deposition is performed by
2 magnetron sputtering at a working gas pressure of greater than about 10 mT.

3 28. The method as set forth in claim 21, wherein the deposition is performed by
4 ion plating at a working gas pressure of greater than about 200 mT.

5 29. The method as set forth in claim 20, wherein at least one of the metals is an
6 anti-microbial metal and wherein the material is formed with sufficient atomic disorder that
7 atoms, ions, molecules or clusters of the anti-microbial metal are released on a sustainable
8 basis.

9 30. The method as set forth in claim 21, 23 or 27, wherein at least one of the
10 metals is an anti-microbial metal and wherein the material is formed with sufficient atomic
11 disorder that atoms, ions, molecules or clusters of the anti-microbial metal are released on a
12 sustainable basis.

13 31. The method as set forth in claim 20, wherein a composite coating is formed by
14 co-, sequentially or reactively depositing a first metal in a matrix with atoms or molecules of
15 a different material from the first metal such that atomic disorder is created in the matrix.

16 32. The method as set forth in claim 31, wherein the first metal is an anti-microbial
17 metal and wherein the different material is atoms or molecules reactively deposited into the
18 matrix from the working gas atmosphere during deposition.

19 33. The method as set forth in claim 31, wherein the first metal is an anti-microbial
20 metal and wherein the different material is atoms or molecules selected from oxides, nitrides,
21 carbides, borides, sulphides and halides of an inert biocompatible metal.

22 34. A method of forming an antimicrobial coating on a device intended for use in
23 contact with an alcohol or water based electrolyte, comprising:

1 depositing a coating containing an anti-microbial metal on the surface of the
2 device by vapour deposition to provide a thin film of the metal having atomic disorder such
3 that the coating, in contact with an alcohol or a water based electrolyte, provides a sustained
4 release of the metal ions, atoms, molecules or clusters into the alcohol or water based
5 electrolyte at a concentration sufficient to provide a localized anti-microbial effect.

6 35. The method as set forth in claim 34, wherein the deposition is performed by
7 a physical vapour deposition technique selected from vacuum evaporation, sputtering,
8 magnetron sputtering or ion plating, under conditions which limit diffusion during deposition
9 and which limit annealing or recrystallization following deposition.

10 36. The method as set forth in claim 35, wherein the deposition is performed such
11 that the ratio of the temperature of the surface being coated to the melting point of the metal
12 is maintained at less than about 0.5.

13 37. The method as set forth in claim 36, wherein the deposition is performed such
14 that the angle of incidence of the coating flux on the medical device to be coated is less than
15 about 75°.

16 38. The method as set forth in claim 36 or 37, wherein the deposition is performed
17 by arc evaporation at an ambient or working gas pressure of greater than about 0.01 mT.

18 39. The method as set forth in claim 36 or 37, wherein the deposition is performed
19 by gas scattering evaporation at a working gas pressure of greater than about 20 mT.

20 40. The method as set forth in claim 36 or 37, wherein the deposition is performed
21 by sputtering at a working gas pressure of greater than about 75 mT.

22 41. The method as set forth in claim 36 or 37, wherein the deposition is performed
23 by magnetron sputtering at a working gas pressure of greater than about 10 mT.

1 42. The method as set forth in claim 36 or 37, wherein the deposition is performed
2 by ion plating at a working gas pressure of greater than about 200 mT.

3 43. The method as set forth in claim 36 or 37 wherein the metal is selected from
4 the group consisting of Ag, Au, Pt, Pd, Ir, Sn, Cu, Sb, Bi, and Zn or an alloy or compound
5 containing one or more of these metals.

6 44. The method as set forth in claim 36 or 37 wherein the metal is Ag, Au or Pd
7 or an alloy or compound containing one or more of these metals.

8 45. A medical device intended for use in contact with an alcohol or water based
9 electrolyte having an anti-microbial coating on its surface, comprising:

10 a medical device formed of a substantially bioinert structural material; and
11 an anti-microbial coating formed on the surface of the medical device, said
12 coating being formed from one or more anti-microbial metals and having sufficient atomic
13 disorder such that the coating, in contact with an alcohol or water based electrolyte, provides
14 a sustained release of the metal ions, atoms, molecules or clusters into the alcohol or water
15 based electrolyte at a concentration sufficient to provide a localized anti-microbial effect.

16 46. The medical device as set forth in claim 45, wherein the deposition is performed
17 by a physical vapour deposition technique selected from vacuum evaporation, sputtering,
18 magnetron sputtering or ion plating.

19 47. The medical device as set forth in claim 46, wherein the metal is selected from
20 the group consisting of Ag, Au, Pt, Pd, Ir, Sn, Cu, Sb, Bi, and Zn or alloys or compounds
21 containing one or more of said metals.

22 48. The medical device as set forth in claim 46, wherein the metal is Ag, Au or Pd
23 or an alloy or compound containing one or more of these metals.

1 49. The material as set forth in claim 6, wherein the coating is a composite coating
2 formed from at least one first metal, which is the metal to be released, in a matrix containing
3 atoms or molecules of a different material from the first metal, the atoms or molecules of the
4 different material creating atomic disorder in the matrix.

5 50. The material as set forth in claim 49, wherein the different material is selected
6 from reacted species of the first metal or metal compound; absorbed or trapped atoms or
7 molecules of oxygen, nitrogen, hydrogen, boron, sulphur and halogen; and a second metal.

8 51. The material as set forth in claim 50, wherein the first metal is an anti-microbial
9 metal and the different material is selected from oxides, nitrides, hydrides, halides, borides,
10 and carbides of an anti-microbial or a second metal; and absorbed or trapped atoms or
11 molecules containing oxygen, nitrogen, hydrogen, boron, sulphur and halogen.

12 52. The material as set forth in claim 49, wherein the first metal is an anti-microbial
13 metal and the different material is an oxide, nitride, boride, sulphide, halide or hydride of an
14 inert metal selected from Ta, Ti, Nb, V, Hf, Zn, Mo, Si, and Al.

15 53. The material as set forth in claim 49, comprising silver oxide, silver metal and
16 optionally absorbed or trapped atoms or molecules containing oxygen, nitrogen, hydrogen,
17 boron, sulphur and halogen.

18 54. The method as set forth in claim 18, wherein the modified material is a
19 composite coating formed by co-, sequentially or reactively depositing a first metal in a matrix
20 with atoms or molecules of a different material from the first metal such that atomic disorder
21 is created in the matrix.

22 55. The method as set forth in claim 53, wherein the first metal is an anti-microbial
23 metal and wherein the different material is selected from atoms or molecules containing

1 oxygen, nitrogen, hydrogen, boron, sulphur and halogen absorbed or trapped in the matrix
2 from the atmosphere of the vapour deposition.

3 56. The method as set forth in claim 54, wherein the first metal is silver and the
4 different material is selected from atoms or molecules containing oxygen, nitrogen, hydrogen,
5 boron, sulphur and halogen.

6 57. The method as set forth in claim 55, wherein the first metal is an anti-microbial
7 metal and wherein the different material is an oxide, nitride, carbide, boride, halide, sulphide
8 or hydride of an inert metal selected from Ta, Ti, Nb, V, Hf, Zn, Mo, Si and Al.

9 58. The method as set forth in claim 57, wherein the first metal is silver and the
10 different material is an oxide of Ta, Ti or Nb.

INTERNATIONAL SEARCH REPORT

PCT/CA 93/00201

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)⁶

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61L29/00; C23C14/14; B22F9/04; C22F1/00
C22C45/00**II. FIELDS SEARCHED**Minimum Documentation Searched⁷

Classification System	Classification Symbols
Int.Cl. 5	A61L ; C23C ; B22F

Documentation Searched other than Minimum Documentation
to the extent that such Documents are included in the Fields Searched⁸**III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹**

Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	GB,A,2 073 024 (NATIONAL RESEARCH DEVELOPMENT CORPORATION) 14 October 1981 cited in the application see page 3, line 57 - line 122; claims 1,8,14,21,31,42,43 ---	1,2, 5-10, 18-22, 29,30, 34-36, 43-48
X	JOM vol. 41, no. 6, June 1989, WARRENDALE US pages 12 - 17 FROES ET AL. 'Nanocrystalline metals for structural applications' See pages 12-13, section "Synthesis"; Table I ---	1-20,49, 54
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¹⁰ Special categories of cited documents:¹⁰ "A" document defining the general state of the art which is not
considered to be of particular relevance¹⁰ "E" earlier document but published on or after the international
filing date¹⁰ "L" document which may throw doubts on priority claim(s) or
which is cited to establish the publication date of another
citation or other special reason (as specified)¹⁰ "O" document referring to an oral disclosure, use, exhibition or
other means¹⁰ "P" document published prior to the international filing date but
later than the priority date claimed¹⁰ "T" later document published after the international filing date
or priority date and not in conflict with the application but
cited to understand the principle or theory underlying the
invention¹⁰ "X" document of particular relevance; the claimed invention
cannot be considered novel or cannot be considered to
involve an inventive step¹⁰ "Y" document of particular relevance; the claimed invention
cannot be considered to involve an inventive step when the
document is combined with one or more other such docu-
ments, such combination being obvious to a person skilled
in the art.¹⁰ "A" document member of the same patent family**IV. CERTIFICATION**

Date of the Actual Completion of the International Search

11 AUGUST 1993

Date of Mailing of this International Search Report

20.08.93

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

PATTERSON A.M.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	EP,A,0 415 206 (YOSHIDA KOGYO) 6 March 1991 see column 2, line 57 - column 4, line 24 -----	1-3,5-7, 10,18-28
X	TECHNISCHE MITTEILUNGEN KRUPP no. 2, November 1989, ESSEN DE pages 69 - 76 SCHLUMP ET AL 'Nanocrystalline materials by mechanical alloying' See whole document -----	1,2,4, 10-13

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

CA 9300201
SA 73911

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82